Flow-pulse response: a new method for the characterization of ventricular mechanics

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HUNTER, WILLIAM C., JOSEPH S. JANICKI, KARL T. WEBER, AND ABRAHAM NOORDERGRAAF. *Flow-pulse response: a new method for the characterization of ventricular mechanics.* Am. J. Physiol. 237(3): H282–H292, 1979 or Am. J. Physiol.: Heart Circ. Physiol. 6(3): H282–H292, 1979.—To determine the mechanical properties of the left ventricle as a pump, we developed a new technique based on impulse-response concepts. In 11 isolated canine hearts contracting isovolumetrically, steplike changes in ventricular volume (ΔV = 1–3 ml) were produced by flow pulses lasting 35–50 ms; such steps could be applied at any phase of systole. The resultant change in ventricular pressure (ΔP) between the perturbed beat and the preceding undisturbed beat was examined during the time of the pulse and the remainder of contraction. The ratio $\Delta P/\Delta V$, a measure of ventricular viscoelasticity, varied throughout systole in characteristic patterns. Following a volume step early in systole, $\Delta P/\Delta V$ increased steadily during contraction (max values, 3.6–11 mmHg/ml). A volume step imposed late in systole, however, produced a bimodal $\Delta P/\Delta V$ with the first transient peak in phase with the flow pulse. Analyzing these patterns revealed that the mechanical components contributed differently to $\Delta P/\Delta V$ depending on the time of the flow pulse: for early pulses, elasticity dominated; for late pulses, a resistive component was more evident. Using pulse-response measurements, we could predict the course of ventricular pressure during ejections having arbitrary flow contours. Measured and predicted pressures agreed within 15%. Thus, the flow-pulse technique provides a comprehensive method to study ventricular mechanical properties.

ventricular systolic elasticity; ventricular source resistance; pump function; isolated canine heart

WHEN THE HEART IS VIEWED as a pump, characteristic properties such as elasticity (18) and resistance (9) describe the mechanical behavior of its ventricles. These properties refer to the internal mechanics of each ventricle, considered independent of its vascular load. Elasticity, for example, reflects the degree to which changes in ventricular volume will alter ventricular pressure (23–25), whereas resistance describes how different rates of ejection influence ventricular pressure (6, 9, 20). Furthermore, the collective mechanical properties of the ventricle offer an insight into the functional state of its myocardium, which is independent of its load (10, 21, 25).

The mechanical properties are also fundamental to understanding the coupling between each ventricle and its vascular load (8, 9, 17). For example, while the left ventricle faces an external load from the systemic circulation, the mechanical properties of the myocardium represent an internal load. Together the external and internal loads form the total load which determines the flow and volume ejected from a given filling volume. The external load due to the impedance of either the systemic or pulmonary vascular beds have been adequately characterized (17). However, detailed studies of the coupling between the heart and circulation await further clarification of each ventricle as a pump.

In previous investigations the definitions of elastic and resistive ventricular properties have varied considerably (6, 9, 24, 27). None have been wholly satisfactory. A particular problem arises because these mechanical properties may be changing rapidly during systole, so that some traditional concepts are invalid (12). In addition, many previous methods were incomplete and restricted to measuring only one aspect of the mechanical properties. Consequently, we developed an approach that emphasizes the variation of mechanical properties during contraction. Our goal was a comprehensive method which would measure all the significant mechanical properties of the myocardium. It is the purpose of this report to introduce this new method, the flow-pulse response, and to describe the mechanical properties that were found for the left ventricle of an isolated canine heart contracting isovolumetrically.

Theoretical background. The mechanical properties of the myocardium are revealed by the changes they produce in ventricular pressure when the ventricle is subjected to different flows and volumes (8, 17). To analyze these effects, we dissected ejection into small portions. Each portion was a rounded steplike decrease in volume produced by restricting flow to a quick pulse (Fig. 1). Aside from this volume step, the ventricle contracted isovolumetrically. Such limited withdrawals were performed at different times throughout systole. As the flow pulses represented partial ejections, the sum of such pulses would simulate physiological ejection. The partition of systole into time intervals was necessary to reveal variations in the mechanical properties of the ventricle during contraction. In fact, the flow-pulse technique was selected from an array of engineering identification techniques because it could deal with time-varying behavior (11, 12). It is a modification of the impulse-response method.

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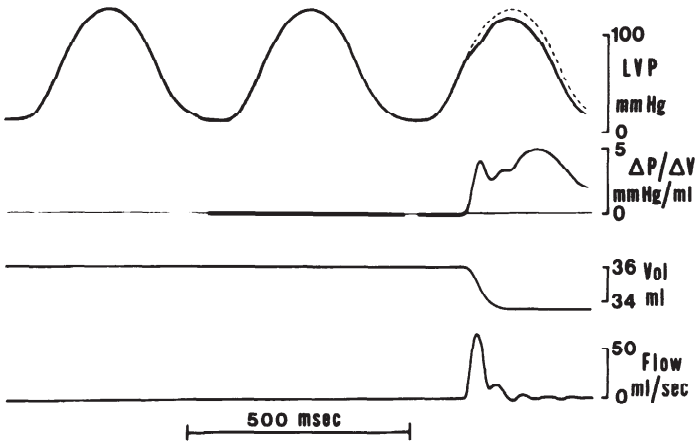

FIG. 1. Typical data illustrating a pulse-response test that consisted of two isovolumetric control beats followed by a perturbed beat. A flow pulse (withdrawal) was applied in midsystole and both volume (Vol) and left ventricular pressure (LVP) decreased. For comparison, the pressure in the previous isovolumetric beat (*broken line*) is shown superimposed on the perturbed beat. The instantaneous difference in pressure between the isovolumetric and pulsed beats (ΔP) divided by the total amplitude of the volume step (ΔV) was the normalized response we studied (ΔP/ΔV). To verify a steady control state, the instantaneous difference in pressure between the two control beats was also examined for deviations from zero.

When applying this method, only one volume step is inserted during a single contraction. The response observed is the change in ventricular pressure produced by the volume step both during the flow pulse and throughout the remainder of the contraction. Figure 1 illustrates a typical volume step and flow pulse and the manner in which changes in ventricular pressure were calculated. For a complete picture it is necessary to study a set of individual contractions in which the individual volume steps are inserted at times varying uniformly throughout systole. In each of those contractions the change of ventricular pressure from that of the preceding control beat (without a volume step) can be determined. This set of changes in pressure constitute the fundamental units of the flow-pulse response.

By analyzing these sets of ventricular pressure responses it is possible to describe the time-dependent nature of ventricular viscoelastic properties. Both resistive (viscous) and elastic components can be distinguished. The resistive component contributes to the observed change in pressure during the flow pulse itself, while the elastic component sustains the pressure change (proportional to the volume change) throughout the remainder of the contraction. Dividing the observed pressure change by the volume step gives a measure of the magnitude of the elastic component.

The pulse-response technique is best suited for describing linear behavior. Linearity, here, implies that the pressure change varies in proportion to the amount of volume withdrawn. Although ejection is normally unidirectional, in cases where volume is added to the ventricle, linearity would also require a proportional response in the reverse direction. For small perturbations most systems respond linearly (incremental linearity), and therefore, the volume steps were limited to 3 ml. Direct tests of linearity were conducted over this volume range and the results are included below.

METHODS

Biological preparation and mechanical system. To achieve control of ventricular volume and to produce narrow flow pulses, an isolated canine heart preparation in conjunction with an electrohydraulic servo system was used. Both the biological preparation and the mechanical servo control have been described in detail elsewhere (13), and are only briefly reviewed here.

Following several preliminary experiments, 11 successive hearts were studied. All animals were anesthetized with sodium pentobarbital (30–40 mg/kg iv). Each isolated heart was perfused at a constant aortic pressure of 100 ± 5 mmHg by oxygenated blood through the cross circulation with another dog. Bipolar pacing electrodes were sewn to the right atrium and sump lines were inserted into each ventricle at the apex. All hearts were studied with their pericardium intact.

To control the volume of the left ventricular chamber, a compliant latex balloon was positioned in the ventricle through the mitral orifice after the chordae tendineae of the mitral valve had been severed. The balloon was attached to a cannula and coupled to the hydraulic servo unit (Fig. 2). Forces generated by the actuator result in the movement of the piston thereby producing alterations in ventricular volume, which are measured by sensing the position of the piston with a linear potentiometer (resolution, 0.2 ml). To produce a flow pulse, the actuator was electronically signaled to rapidly shift the piston within 35–50 ms to a new position. Oscillations following such a pulse were mechanically damped by having viscous fluid, on the actuator side of the piston, pass through a narrow-orifice valve.

Pulse flow was measured using an extracorporeal electromagnetic probe in conjunction with a gated-sine wave flowmeter filtered at 100 Hz. Intraventricular pressure inside the ventricular balloon was measured by a Statham transducer (P23Gb) through a Teflon catheter (natural frequency 146 Hz and damping ratio 0.21). The catheter was positioned away from the region of high flow velocity at the mitral orifice so that changes associated with intraventricular pressure gradients required to accelerate and decelerate fluid during the pulse would

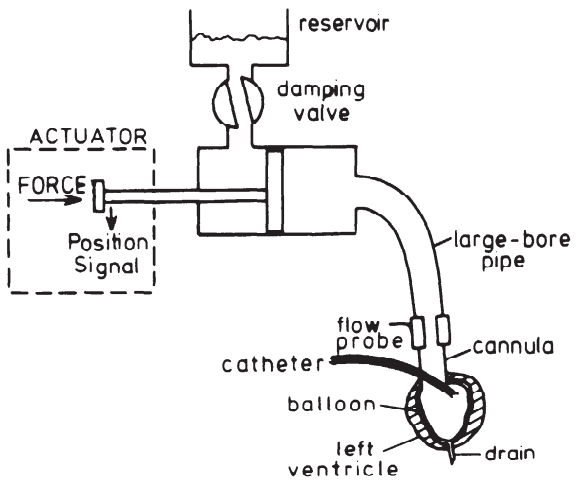

FIG. 2. Schematic of the hydraulic system used to control ventricular volume and to produce the flow pulses. See text for details.

not significantly influence the pressure recording. The magnitude of such transients was determined at the conclusion of several experiments following potassium arrest and found to be smaller than ±1 mmHg/ml.

Protocol. Throughout the experiment the heart contracted isovolumetrically except for those contractions perturbed by a flow pulse. After establishing an isovolumetric steady state, a single flow pulse was applied at the desired stage of systole (Fig. 1). The amplitude of the pulse was adjusted so that ventricular volume and pressure changed on the order of 5–15%. The volume changes ranged from 1.5 to 3 ml; flow pulses were 35–50 ms in duration. Following the pulse the contraction continued at the new volume until being restored during the subsequent beat. Another pulse was not generated until 5 s had elapsed, allowing for any subtle changes in mechanical behavior to dissipate and for the reestablishment of the original isovolumetric steady state. The original state was verified by examining the peak isovolumetric pressure attained for the given diastolic volume.

To completely describe the mechanical properties of the contracting ventricle, flow pulses were applied at varying times during systole. Pulse onset time (relative to the pacing stimulus) was altered between pulse tests by means of an electronic delay unit that controlled the time from pacing stimulus to initiation of a flow pulse; amplitude and shape of the pulses remained constant. The first pulse was applied near end diastole (i.e., at time of QRS), and subsequent pulses were obtained by delaying in steps of 20 ms until 40 ms beyond the time at which peak isovolumetric pressure occurred. The sequence was repeated by applying the pulses at the same intervals, but in reverse order. Typically pulse data were obtained at 10 discrete times during systole; an average of 5 min was required to complete such a series. At least one duplicate measurement was performed at each delay time in each sequence.

Computation of pulse response. An example of a single pulse-response test is given in Fig. 1. As volume decreased, here approximately 2.4 ml, ventricular pressure was attenuated when compared to the preceding isovolumetric beat and remained so throughout the rest of systole. This reduction in pressure is easier to visualize when the control isovolumetric beat (broken line) is superimposed on the perturbed beat. The pulse response ($\Delta P/\Delta V$) was computed from the difference between perturbed and control pressures (ΔP) divided by the total change in volume (ΔV). Thus, the physical dimensions of the pulse response are equivalent to those of an elastic element. Assuming linearity of the ventricular response, normalization by ΔV would also cancel any variability in the response due to varying volume steps. $\Delta P/\Delta V$ is positive because a decrease in pressure accompanies a decrease in volume.

In computing the pulse response it is assumed that if no pulse had been applied, ventricular pressure would have followed exactly the same course as in the previous control beat. To estimate the accuracy of this assumption, we computed the pressure difference between two control beats immediately preceding a perturbed beat (Fig. 1) and divided this difference by the volume step in the following pulsed beat. Figure 3 includes three examples of these unfiltered $\Delta P/\Delta V$ base lines. These tracings measured the noise signal in the pulse response arising from biological variability between beats, electronic instrumentation, and recording noise. After filtering, the standard deviation of the base-line signals (averaged throughout the systolic phases from all acceptable tests on any one heart) was always less than 0.2 mmHg/ml (range, 0.09–0.16). Arrhythmias or other deviations from steady state, evident in any single $\Delta P/\Delta V$ base-line tracing, were grounds for rejecting the pulse response associated with a particular sequence of three beats. If the filtered standard deviation was greater than 0.3 mmHg/ml, the data from that set were seriously questioned and usually discarded. Approximately 5% of the pulse tests were rejected for this reason.

Data were recorded on FM magnetic tape and then digitized at a sampling rate of 500 Hz. Following computation of the pulse response ($\Delta P/\Delta V$), additional signal conditioning included digital filtering (attenuation above 25 Hz) and averaging duplicate pulse tests.

RESULTS

Time course of pulse response. The contour of $\Delta P/\Delta V$ was found to be a function of pulse onset time, confirming that the viscoelastic properties of the left ventricle are time varying. An example is given in Fig. 3. Shown are three $\Delta P/\Delta V$ curves corresponding to flow pulses initiated during early (Fig. 3*A*), middle (Fig. 3*B*) and late (Fig. 3*C*) systole. In addition, for comparison purposes, the control and perturbed LVP curves are superimposed. In *panel A*, $\Delta P/\Delta V$ is seen to increase steadily with ventricular pressure; however, its maximum value is attained when pressure was rapidly falling. In contrast, a biphasic form is evident for pulses imposed during midsystole (*panel B*). The first peak was observed to coincide with the flow pulse, while the remainder of the response was attenuated but similar in shape to that in *panel A*. A pulse initiated near peak pressure elicited an even stronger biphasic response (*panel C*). Again, as in *panel B*, the first component was in phase with the flow pulse; however, following the pulse $\Delta P/\Delta V$ declined almost to zero. Corresponding to this decline and as shown in the

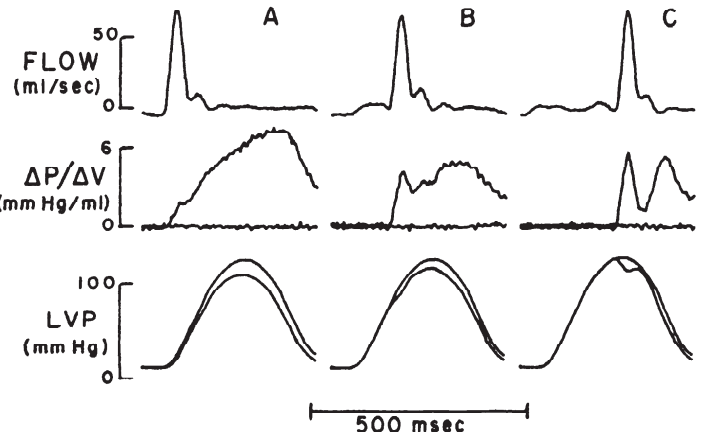

FIG. 3. Pulse responses ($\Delta P/\Delta V$) and their corresponding superimposed control and perturbed ventricular pressures (LVP) obtained during three phases of systole—early (*A*), middle (*B*), and late (*C*). The $\Delta P/\Delta V$ contour is seen to be a function of pulse onset time.

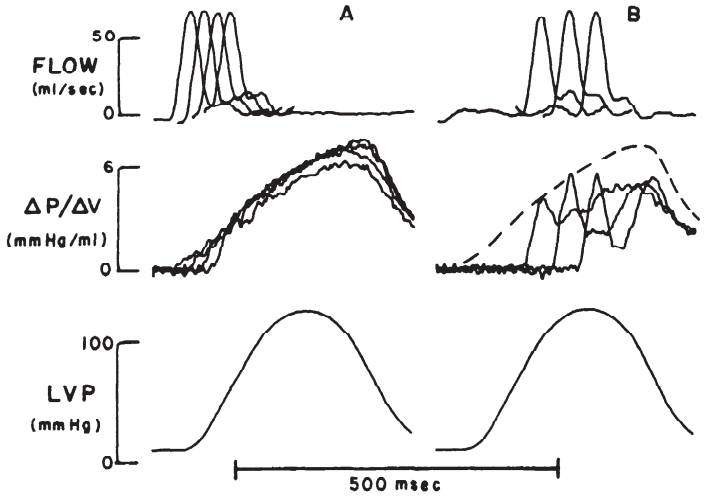

FIG. 4. Comparison of superimposed pulse responses (ΔP/ΔV) for flow pulses applied early (*A*) and late (*B*) in systole. The control LVP curves are included for orientation. Dashed line in *panel B* is the common response curve near which all early responses fell in *panel A*.

superimposed left ventricular pressure tracings in *panel C*, perturbed pressure rebounded almost to the control level despite the fact that more than 2 ml had been removed. The second transient ΔP/ΔV component peaked when ventricular pressure was rapidly relaxing.

To directly compare the individual responses to pulses initiated at different onset times, data from Fig. 3 and additional pulses were superimposed into two groups (*panels A* and *B*) in Fig. 4. The dramatic change in the response of the left ventricle from early to late systole is apparent. Figure 4*A* indicates that the early responses superimposed so as to define a common curve, irrespective of when the flow pulse was applied. By one-third of the time from end diastole to peak pressure, however, responses were beginning to deviate from the common curve. Figure 4*B* compares the common response (dashed line) to the bimodal behavior observed for pulses applied later in systole. The initial transient, always in phase with flow, increased corresponding to the larger ventricular pressure present during the pulse time, and the decline following these first peaks was closer to zero as the pulses occurred later.

Even though the form of ΔP/ΔV varied between pulses applied early and late in systole, this variation was gradual with each successive 20-ms delay in pulse timing. This continuity can be seen in Fig. 5, which presents an overlay of the response to pulses spaced every 20 ms throughout systole. Data from Figs. 3 and 4 are included.

Figures 3, 4, and 5 have presented data from one experiment under the same steady-state isovolumetric conditions. A similar behavior was observed in all experiments regardless of the level of ventricular performance. Figure 6 presents examples of complete sets of responses obtained in two other experiments in which peak isovolumetric pressures were notably different. Although the qualitative form held in all cases, differences in performance did alter the magnitude of the total response. One estimate of magnitude is given by the maximum value of ΔP/ΔV, which was 7.6 mmHg/ml for the data in Fig. 5 and 5.1 and 9.5 mmHg/ml for the two experiments in Fig. 6. For all experiments, the peak ΔP/ΔV values ranged from 3.6 to 11 mmHg/ml.

Influence of pulse width. To test how the form of the flow pulses affected the form of the pressure response, we also utilized wider flow pulses in addition to the basic narrow pulse. In both cases the volume steps were equal and the two pulses began at the same phase of systole. However, for a wider pulse the velocities of flow were smaller and the volume was changing over a longer time interval.

When the flow pulses began at the onset of systole, the difference in response between wide and narrow pulses was minimal (Fig. 7*A*). Width had a stronger effect on pulses applied later in systole (Fig. 7*B*). The pressure response simultaneous with the peak flow was reduced roughly in proportion to the decrease in flow velocity. After the flows had returned to near zero, ΔP/ΔV was still consistently smaller for wider flows despite identical volume steps.

Evaluating linearity. To test the incremental linearity

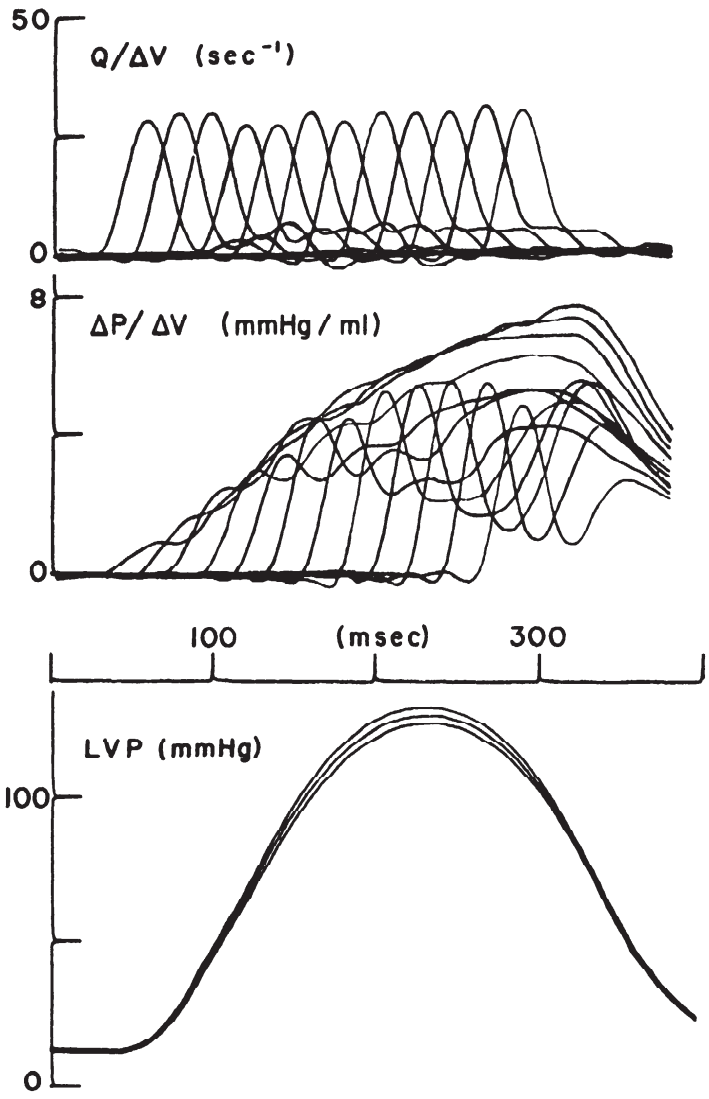

FIG. 5. A complete set of superimposed pulse responses (ΔP/ΔV) throughout systole. Normalized flow pulses (Q/ΔV) and ΔP/ΔV were filtered and duplicates were averaged. Also shown is the average ± SD of all control pressure curves (LVP) obtained for this set.

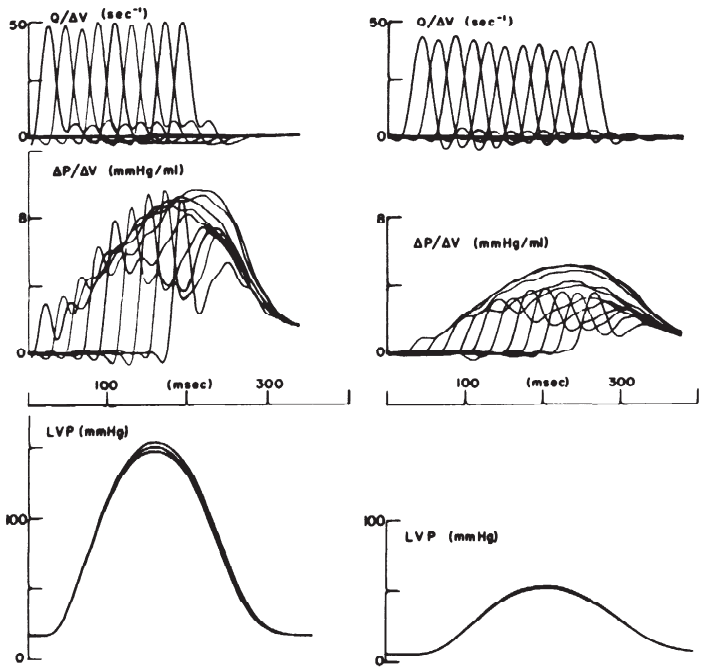

FIG. 6. Complete set of superimposed responses from two experiments. Symbols same as in Fig. 5. The qualitative form is the same despite the differences in LVP.

of the ventricular flow-pulse response, volumes of varying amounts (1–3 ml) were either withdrawn or infused. For pulses applied early in systole, Fig. 8*A* shows flow pulses directed either into or out of the ventricle. In either direction ΔV for the larger flow was twice that for the smaller flow. The superimposed pressure traces include four perturbed beats and their common isovolumetric control contractions (center trace). Removing twice the volume caused twice the pressure drop from control. Similarly, infusing volume caused the pressure to rise to the same extent it had dropped during withdrawal for the same volume. Computing ΔP/ΔV (*panel B*, data from a different experiment) demonstrated that the form of the pulse response was independent of the magnitude or direction of volume change over the range tested (± 3 ml). The results from four other experiments (each symbol denotes an experiment) in which incremental linearity was examined are summarized in *panel C* as a graph of normalized ΔP vs. ΔV. To derive normalized ΔP, each pressure difference signal was averaged over time, and the mean pressures were scaled so the regression lines from all four hearts would superimpose. In this way only the deviations from linearity are plotted, and the resulting graph emphasizes that these deviations were minimal.

A directionally linear response was not the case, however, when pulses were applied near peak pressure, as can be seen in Fig. 9. Although the component in phase with flow did reverse for opposite flows (Fig. 9*A*), as expected for a linear response, its magnitude tended to be slightly smaller for infusions than withdrawals (Fig. 9*B*). The major directional effect occurred during relaxation. The second transient decrease in pressure following withdrawal was not mirrored by a second transient increase following infusion. Instead, the second transient was missing or inverted, indicating no pressure increase or even a fall in pressure following infusion.

Although comparing flows into or out of the ventricle revealed directional differences, an approximately linear response was maintained in each direction for varying pulse amplitudes. Figure 9*B* shows the response to pulses applied late in systole in both directions. A pair of withdrawals produced nearly identical ΔP/ΔV signals, although one had a pulse volume twice that of the other. The same observation also held for infusions. However, the divergence between the withdrawal and infusion pairs illustrates the directional difference. A plot of the average ΔP vs. pulse volume (Fig. 9*C*) emphasizes that the nonlinear shift occurred primarily when switching the direction of volume change.

Prediction of ventricular pressure. Once pulse responses have been measured for pulses spanning all of

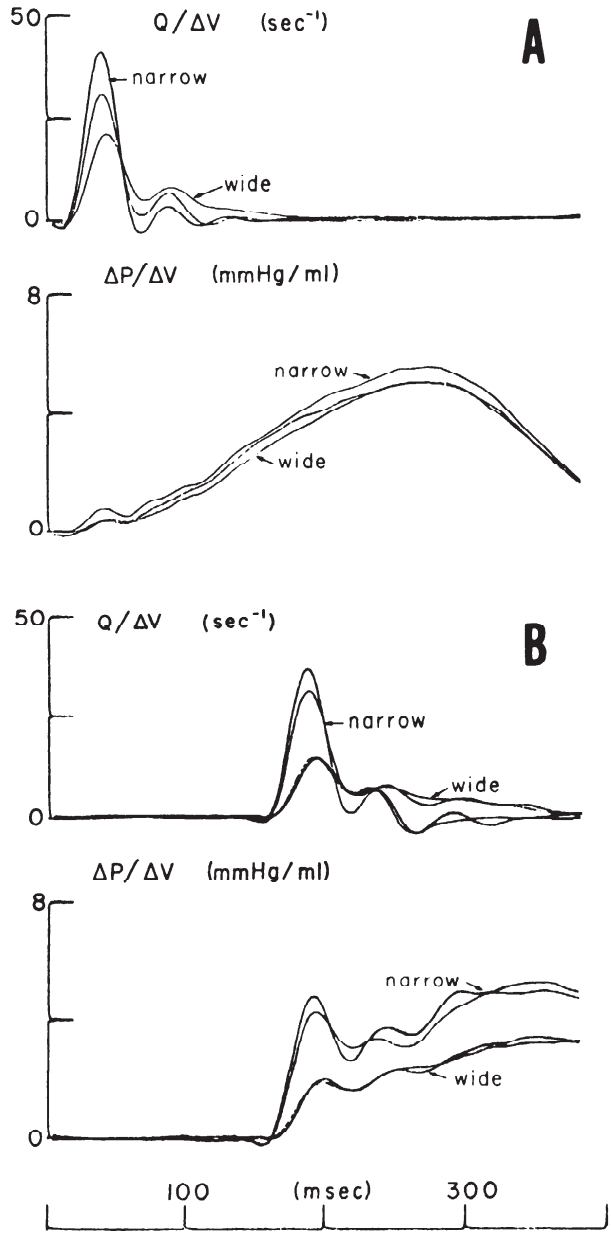

FIG. 7. Influence of width of flow pulses. Early in systole (*A*), width had little effect on the pulse response (ΔP/ΔV). Later in systole (*B*), a narrow pulse produced greater response, both during the pulse and throughout systole. This difference was independent of the volume-step amplitude: the normalized responses to steps of 2.2 or 3.0 ml were nearly identical.

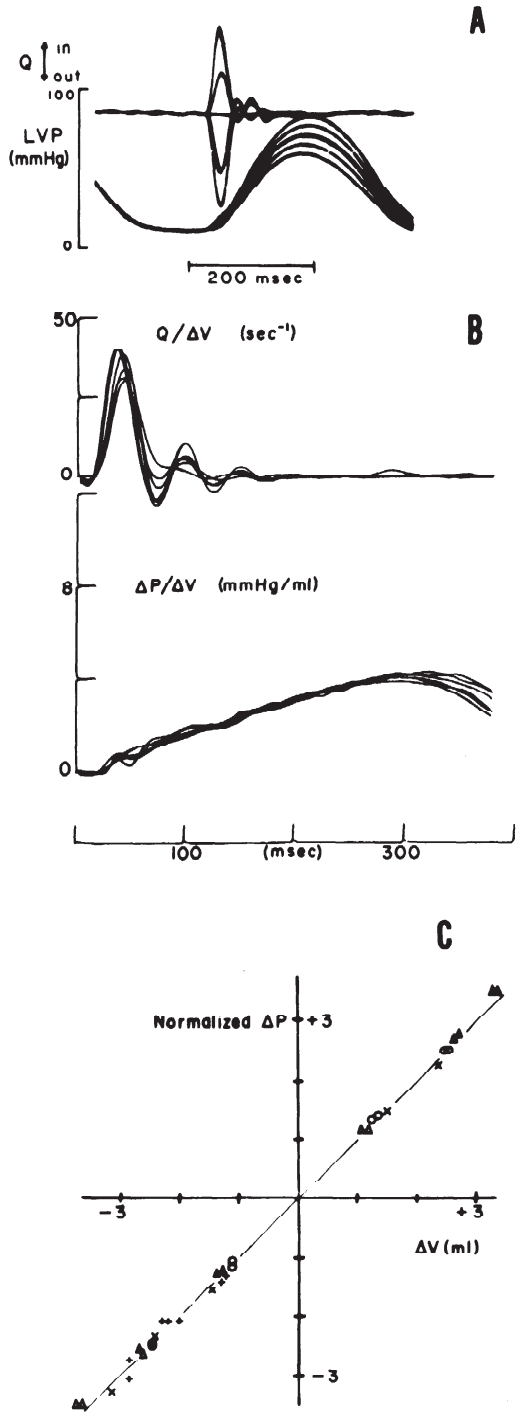

FIG. 8. *A:* effect on LVP of changing flow-pulse (Q) amplitude and direction when the pulse was applied early in systole. Center LVP trace is control and the larger Q amplitudes correspond to the greater LVP changes. *B:* pulse response (ΔP/ΔV) and normalized flow pulse (Q/ΔV) computed for pulses of varying amplitude and direction. All Q/ΔV are indicated positive because flow was normalized (see text). Raw data on which these curves were based is similar to *panel A* but from another heart. *C:* relationship between time-averaged pressure difference (ΔP) and pulse volume (ΔV) for early pulses. Each symbol represents data from a different experiment. ΔP has been further normalized by the slope of the regression line through the origin for each experiment.

systole, we can use that data to predict quantitatively ventricular pressure for any given form of ejection flow. The first step in the prediction procedure is to mathematically adjust the amplitude of the flow pulses so that, when summed together, they will match the contour of the ejection flow. After a few repeated adjustments of flow amplitudes, weighted sums of flow pulses conform very closely to almost any form of ejection flow (Fig. 10, top row). Next, the individual ΔP/ΔV responses are scaled by the same factors used for the flow pulses. These scaled responses are summed to predict the pressure difference between an isovolumetric beat and an ejecting contraction having the composite flow pattern.

To test the predictive aspects of the flow-pulse technique, the measured and predicted pressure changes during arbitrary patterns of ejection flow were compared. Each arbitrary ejection flow was imposed during an

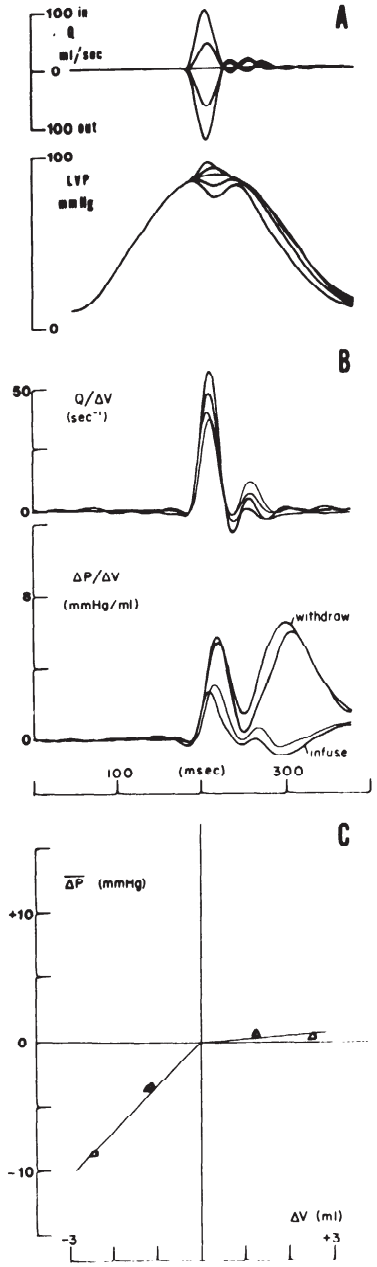

FIG. 9. *A:* similar to Fig. 8 except for the time at which the pulses were applied; here, late in systole. This raw data is the source of computed data in *panels B* and *C*. *B:* for flow pulses late in systole, ΔP/ΔV was dependent primarily on the direction of the flow pulse but not its amplitude. *C:* time-averaged pressure difference ($\overline{\Delta P}$) in response to each pulse is plotted vs. pulse volume (ΔV). Separate regression lines constrained to pass through the origin are shown for infusions and withdrawals.

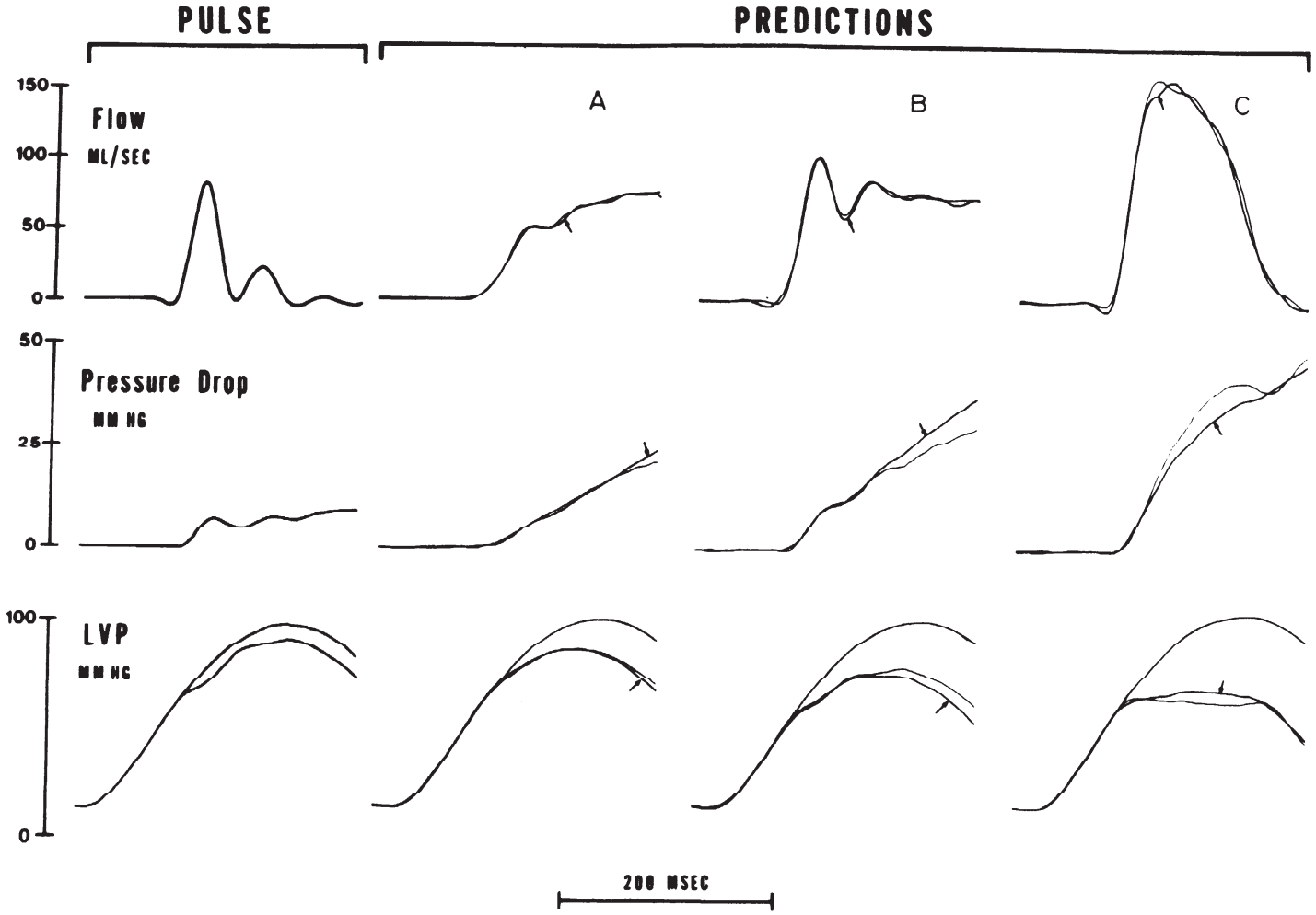

FIG. 10. Predictions based on a set of responses to flow pulses. Pulse: one example from the set of flow pulses. Other pulses had a similar shape and amplitude but were shifted in time. Pressure drop is the difference in pressure between the beat in which volume was withdrawn and the preceding isovolumetric beat. Ventricular pressures (LVP) during these two beats are superimposed below. Predictions: three examples (*A*, *B*, *C*) comparing measured vs. predicted drops in pressure during arbitrary patterns of ejection flow. Arrows indicate the predicted pressure and the flow pattern computed from the sum of suitably scaled pulses.

otherwise isovolumetric steady state so that ventricular conditions were similar during the times of the test flow and the series of flow pulses used for prediction. All predictions for an experiment were based on the same series of pulse responses, which was measured several minutes before the test flows were applied.

Figure 10 presents prediction tests from the same heart having three ejection-flow patterns of widely varying form and amplitude. A single flow pulse and its response are shown in the first column. Following the standard protocol, flow pulses applied at other phases were identical to this one in form and amplitude. Pressure responses to the other individual pulses varied according to the typical pattern (Figs. 3–6) with amplitudes comparable to that shown here. The sums of the scaled flow pulses (indicated by arrows) were almost indistinguishable from the ejection-flow patterns. The predicted fall in pressure from isovolumetric to ejecting contractions (arrows) was compared to the measured pressure drop.

The predicted fall in pressure agreed reasonably well with the measured fall in pressure. Usually, the divergence between the two tended to increase during the phase of relaxation where the predicted fall was greater than that measured (*panels A* and *B*). Before the relaxation phase, disagreements between measured and predicted pressure changes never exceeded 15%. As might be expected, pressures closest to the isovolumetric condition were the most accurately predicted. However, the prediction also held reasonably well even for a flow contour and stroke volume resembling normal ejection (*panel C*).

DISCUSSION

By probing the ventricle with narrow flow pulses, we were able to quantify, in detail, how the time course of pressure during a contraction was related to flow. This relationship could be summarized graphically (see Fig. 5) to document, in a comprehensive way, how each heart responded to ejection. In principle, the response to any conceivable form of ejection, not only pulses, could also be quantified by the pulse-response method because predictions can be based directly on the measurements. Thus, we consider the pulse response to be a general representation of the relation between ventricular pressure and flow. Its general validity may be limited, however, by the range of volume over which the ventricle responds in a sufficiently linear manner.

Because the pulse response gives such a general picture, it provides a complete description of the effective mechanical properties of the ventricle as a pump. By decomposing the pulse response into equivalent mechanical components, we have a method to measure these properties. However, the pulse response provides much more information than just values for viscoelastic elements. It also suggests which mechanical elements are effectively present and how they are arranged. Direct evidence on an arrangement of mechanical elements to represent mechanical properties of the ventricle would be desirable, but it becomes more imperative in light of the uncertainties in cardiac muscle mechanics (1) and in extrapolating muscle properties to the whole ventricle (5). Thus, the pulse response avoids a weakness of other methods (6, 20, 24, 27), which must select elements and assume a priori arrangements before measurements can be made.

Mechanical components of the pulse response. Figure 11 depicts how the decrease in pressure caused by a flow pulse could be broken into elastic and resistive components, plus a third component. The change in pressure (ΔP) due to the resistive component will follow the form of the flow pulse and must return to zero when the pulse has passed. The ΔP due to the elastic component rises as volume changes during the pulse; thereafter, increases in the elastic ΔP reflect increases in the stiffness of the elastic element since volume is constant. The third component is a directional effect: when volume is withdrawn it adds to the decrease in pressure; when volume is infused it subtracts from the expected increase in pressure.

The changing form of the pulse response between early, middle, and late systole reveals a shift in the relative contribution of each component (Fig. 11). The elastic component dominates the response to volume steps applied early in systole, but volume steps occurring later are progressively uncoupled from the elastic element. In contrast, the resistive element becomes progressively larger for later pulses, and the directional component also contributes more. We do not consider the change in the elastic response to be a weakening of the elastic element itself; in fact, the elastic component in response to an early volume step becomes continually stiffer during systole. Rather, the phenomena suggest that the mechanism producing the elastic effect becomes progressively less sensitive to volume changes later in systole.

Comparing differences in ventricular response to pulses of different widths supports this division into mechanical components. The decreased flow amplitude during wider pulses should proportionally reduce the influence of the resistive element on the pulse response. This effect was clearly evident for pulses applied late in systole when the resistive element was dominant; on the other hand, width had much less effect on early pulses, when the resistive element was minimal. Because the elastic element is fully coupled to early volume changes, wide or narrow pulses applied early in systole did not differ in their elastic response. Later in systole, however, wider pulses produced less sustained pressure difference. This observation reflects the decreased sensitivity of the elastic component to later flows, because wider pulses have proportionally more flow at later times.

Missing from the components seen in the pulse response are any effects of a series elastic element (1). If such an element is indeed present in the ventricle, it is so stiff that flow pulses of the width used in this study caused negligible changes in its length. It is possible that more rapid volume steps might uncover a series elastic

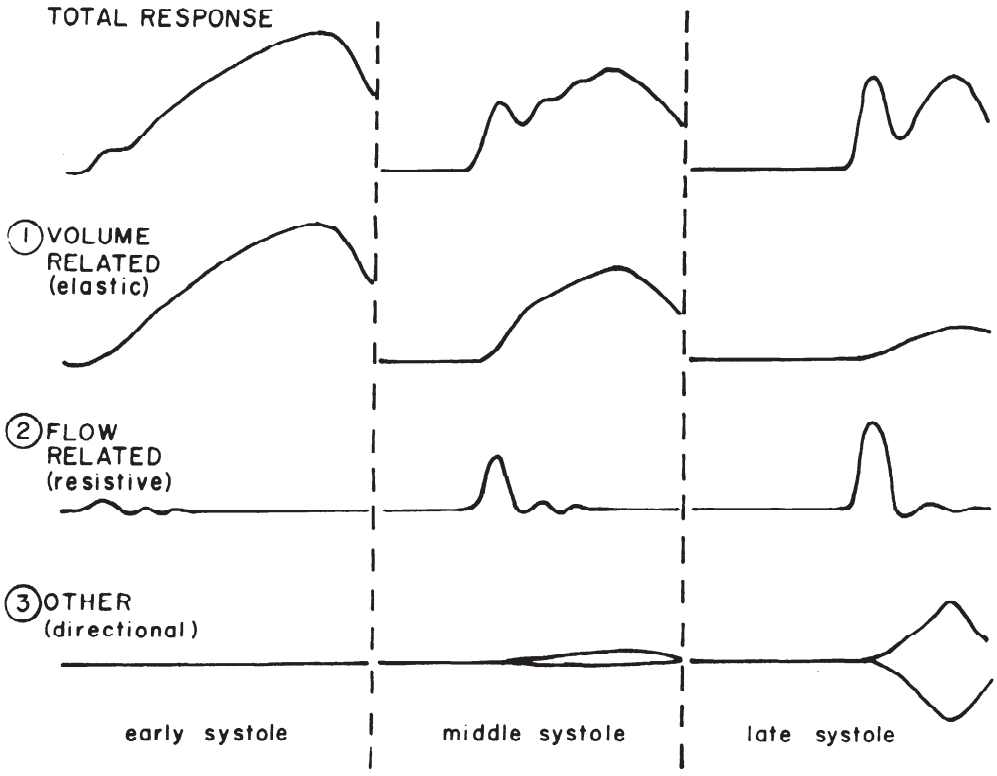

FIG. 11. The pressure differences seen in the pulse responses can be decomposed into three components, sketched in each column below the total response. One component is a resistive effect present only during the flow pulse. Another is an elastic component, which contributes throughout systole following a pulse because of the maintained volume change. The third component is a directional effect indicating the difference in response between infusions and withdrawals. When pulses are applied at different phases of contraction (early, middle, late), the relative magnitude of each component progressively alters.

element (7, 22). Nevertheless, because the pulses used here are rapid enough to describe the details of normal or pathological ejection flow, the present results imply that a series elastic element would play no significant role during ejection.

The mechanical properties of the ventricle as a pump reflect similar properties of cardiac muscle. The resistive component of the pulse response, for example, describes a phenomenon similar to the inverse relationship between force and velocity seen in isolated cardiac muscle (20). As the average velocity of fiber shortening increased during the initial phase of a flow pulse, there was a progressive fall in force. Furthermore, the lower velocities during wider pulses caused less decline in force. The increase in the resistive component as pulses were applied later in systole can also be related to properties of cardiac muscle: the apparent muscle viscosity, measured by small sinusoidal length perturbations, is larger later in systole when developed force is larger (16).

The elastic component of the pulse response reflects the length-dependent property of the myocardium. During the transition from rest to contraction, the force-length relations of the myocardium become much steeper (28), which is consistent with the increase in stiffness which we observed following volume steps at the onset of systole. Second, as the wave of activation spreads across the ventricle, the increasing number of activated fibers would also contribute to increasing the stiffness. When small length changes were applied to cardiac muscle (16), the changes in stiffness were similar to our findings, namely, a steady increase during contraction and a maintained plateau as relaxation began. The maintained stiffness may be the result of length-dependent differences in relaxation (19), which appeared in the isovolumetrically beating ventricle as delays in the timing of peak pressure and relaxation for each increment in volume (Fig. 8*A*).

The elastic component demonstrated a varying sensitivity to volume changes occurring at different times in systole. Early in systole there was little difference, so that the response to volume steps fell along a common curve (Fig. 4*A*). In experiments on cardiac muscle (3), length steps early in systole also produced a common force tracing. However, volume steps applied later in systole produced progressively less pressure change of the elastic sort. This varying sensitivity is difficult to reconcile with the traditional explanation of length-dependent effects in muscle, that is, the overlap of sliding filaments (4). In recent investigations (14), this explanation has been questioned, however, and it is suggested that length-dependent activation and relaxation control a major fraction of the force-length relation. Because activation and relaxation are dynamic, time-varying processes, these phenomena provide a plausible basis for variations in the force-length relation that depend on the timing of length changes.

Although the resistive and elastic components appeared to react linearly over the small range of volume steps that we studied, we attribute the difference between infusions and withdrawals (Fig. 9) to a third, directional component. We assume that this component acts equally during infusions and withdrawals to reduce ventricular pressure below the level expected from the resistive and elastic components alone. This effect is similar to the deactivating influence of fiber displacement (either stretching or shortening), which causes a loss of contractile force in cardiac muscle throughout systole (3, 15). Like deactivation in muscle, the directional component was not seen when volume steps occurred early in systole, but became increasingly evident the later such steps were applied. The deactivating effect in muscle is also proportional to the amount of displacement (15), and this is consistent with our findings. However, the degree of deactivation seen in the pulse response appears to be less than in muscle preparations, perhaps due to the slower speed of our volume displacements. The time course of the directional difference peaked when ventricular pressure was rapidly falling. This timing suggests that there was an earlier onset of relaxation following a later volume step than in an unperturbed beat.

Comparison with other methods. The flow-pulse response was designed to overcome what we perceived to be the limitations of earlier methods for measuring the mechanical properties of the heart. The methods of measuring resistance proposed by Elzinga and Westerhof (9) or Buoncristiani et al. (6) are only able to predict the mean relationship between ventricular pressure and flow. This sacrifices much useful information contained in the pulsatile components. On the other hand, the method of Templeton et al. (25, 27) is confined to the high-frequency range (12). These oscillations are much more rapid than the physiologically significant frequencies in a normal ejection. The measurement of elasticity by Suga and coworkers (23, 24) is also incomplete because it makes no allowance for resistive effects. Their pressure/volume ratio is appropriate only so far as a single elastic component is a valid model of ventricular dynamics. Although more complex models have been proposed (20), they are also constrained by a priori assumptions inherent in selecting a model. Finally, the approach of Abel (2) and Elzinga and Westerhof (8) to measure ventricular source impedance over a range of frequencies is limited because a frequency analysis of impedance is not appropriate for the heart (12).

In contrast, the flow-pulse response has the following advantages: *a*) it emphasizes pulsatile behavior, *b*) it is appropriate when properties vary rapidly with time, *c*) it does not depend on a priori models; *c*) it relies only on the testable assumptions of incremental linearity and superposition, and *e*) it measures all the significant mechanical parameters simultaneously. Because it is comprehensive, the pulse response allows one to predict the time course of ventricular pressure for any systolic loading condition. Many of these advantages stem from the fact that the pulse response is a general description of the left ventricle as a pump.

The pulse response provides more information than other methods; unfortunately it is also more complex. In the present initial phase of research, the additional information concerning the arrangement of mechanical elements is valuable. Later, however, simplified versions of the flow-pulse technique or another method might be sufficient. A second limitation of the pulse technique is the requirement for a highly stable contractile state over

many cycles. Only then can the response to pulses during entirely different beats be legitimately compared. Finally, nonlinear behavior of the ventricle may limit the range of validity of pulse measurements, although our initial tests (see below), have not indicated that such nonlinearity causes large errors.

Despite differences in technique, measurements of elastic and resistive components by others can be compared to our findings. As Suga et al. (23, 24) reported, the pulse response also indicated that ventricular elasticity increases steadily during systole. The range of maximum values of systolic elasticity observed by these investigators was 4–9 mmHg/ml (23, 24). Our findings (4–11 mmHg/ml) are in close agreement with their results. The resistive component of the flow-pulse response can be compared with the findings of Templeton et al. (25, 27), whose high-frequency oscillations would emphasize the resistive component. When Templeton et al. lowered the perturbing frequency (26), $\Delta P/\Delta V$ also fell, and this decrease is compatible with resistive behavior. Their observation that $\Delta P/\Delta V$ increases with ventricular pressure is in accord with the increase in the resistive component noted by our technique for pulses late in systole. Quantitatively, the values for $\Delta P/\Delta V$ reported by Templeton and co-workers (7–13 mmHg/ml at 100 mmHg ventricular pressure) appear higher than our measurements. However, their high-frequency oscillations have an effective pulse width of only 20–30 ms and would therefore be expected to magnify the resistive pressure difference.

Several groups (7, 22) have attempted to withdraw ventricular volume rapidly (within 7–12 ms). For our purposes such abrupt changes did not seem desirable. Abrupt displacements are known to strongly deactivate cardiac muscle for the remainder of a contraction (3, 15). Rapid rates of fluid withdrawal would also require excessive flows and accelerations which, in turn, could introduce spurious components into the pressure response. Consequently, we selected the duration of the flow pulses to be 35–50 ms to match the range of physiological conditions (i.e., the highest significant frequency component of ejection flow being limited to 20–25 Hz). The shape of the flow pulse was similarly designed to be smooth or rounded because a rectangular contour would also favor excessive acceleration. In addition, such a contour more closely approximates the ideal shape for pulses to be summed into composites and therefore to match more closely any probable ejection flow (11).

Incremental linearity and superposition. In addition to describing the mechanical properties of the muscle pump we were also able to apply the flow-pulse response to predict ventricular behavior. For predictions to be valid, however, two basic conditions must be satisfied. The first is incremental linearity. When the amplitude of a flow pulse is halved or doubled, the amplitude of the pressure change should follow in proportion. The second requirement is superposition. Pulse responses are measured when only a single flow pulse is applied during one contraction. Synthesis requires that these individual responses remain the same when the pulses are merged with others in the same beat to form a composite ejection.

Our tests indicated that incremental linearity holds so long as the direction of flow is not reversed. Although there can be significant differences in response between infusions and withdrawals, these directional differences should not hinder predictions under realistic circumstances since systolic flow is normally unidirectional. Whether incremental linearity holds for higher flow amplitudes (>100 ml/s) and larger volume steps (>3 ml) than the range we examined remains to be tested.

Superposition would not be valid if the pulse perturbation itself altered the time course of the mechanical properties during the remainder of the contraction. If this were true, a subsequent pulse in the same beat would see altered properties and thus give a different response than that measured when the pulse was applied individually. However, the agreement between predicted and measured pressures for widely varying ejection flows indicates that deviations from superposition were not large. Thus, although we have suggested that pulse perturbations tend to deactivate the contractile apparatus, such effects do not necessarily impede prediction. The impact of deactivation on prediction is reduced because the pressure difference caused by deactivation is largest during relaxation, where normal ejection flow is small.

The questions of linearity and superposition do require more investigation. The present study was oriented around isovolumetric control beats, with small perturbations in volume around this reference situation. It is encouraging that data based on such isovolumetric contractions could predict the approximate course of pressure during a normal ejection (Fig. 10*C*). However, other experimental conditions should be investigated to provide direct evidence of the influence of the reference state on the response to small perturbations. A particularly appropriate reference would be an average ejecting condition operating in the middle of the physiological range. Because the range of prediction would be narrower, even more accurate predictions might be possible.

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